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COMMUNICATION

Reactivity of (1′*S*)-1-(1′-phenyl-ethyl)-4-hydroxy-piperidin-2-one with Lawesson's reagent

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The study of the reactivity of diasteromeric mixture (1′*S*)-1-(1′-phenyl-ethyl)-4-hydroxy-piperidine-2-one **2** with the Lawesson's reagent in different conditions is described.

Keywords: Lawesson's reagent; molar relation; (1′*S*)-1-(1′-phenyl-ethyl)-4-hydroxy-piperidine-2-one; 5,6-dihydropyridin-2(1H)-thione; 4-mercapto-1-(1′-phenyl-ethyl)-piperidine-2-thione

1. Introduction

2,4-Bis(*p*-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide, commonly known as Lawesson's reagent (LR), is one of the best known thionation reagents, and is normally used to transform ketone or amide function into thione [1–6] and thioamide [7–8], respectively.

In related chemistry, we described in a previous publication the transformation of an enantiopure *trans* bicyclic lactam with LR into the corresponding bicyclic thiolactam, and starting from this compound we carried out the enantioselective synthesis of (−)-dihydropinidine and (+)-indolizidine 167B [9]. In this context, now we investigate the reactivity of the diastereomeric mixture (1′*S*)-1-(1′-phenyl-ethyl)-4-hydroxy-piperidine-2-one **2** with LR in order to prepare useful synthetic intermediates of alkaloids.

2. Results and discussion

(1′*S*)-1-(1′-Phenylethyl)piperidine-2,4-dione **1** was prepared following the methodology reported by Micovic [10]. This compound was then treated with $NaBH_4$ [11] to obtain a

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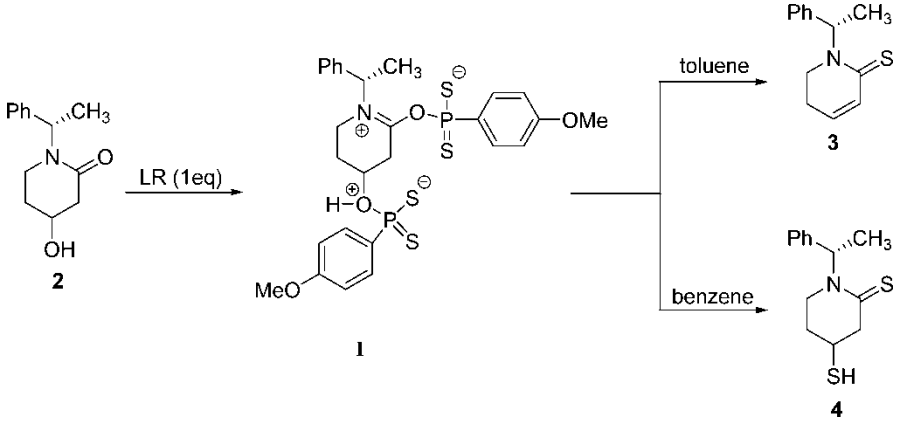
diastereomeric mixture of **2** in a 1:1 ratio and 95% yield. Amide **2** was then treated with the LR using two different procedures.

In the first procedure, the reaction was carried out as in literature [1–8]. To a suspension of LR (1 eq.) either in toluene or benzene [12] was added a solution of diastereomeric isomers **2** (1 eq.) and the reaction mixture was refluxed for 120 h. The reaction in toluene afforded (1′*S*)-1-(1′-phenylethyl)-5,6-dihydropyridin-2(1*H*)-thione **3** in 56%, while in benzene this compound was obtained in 45% yield.

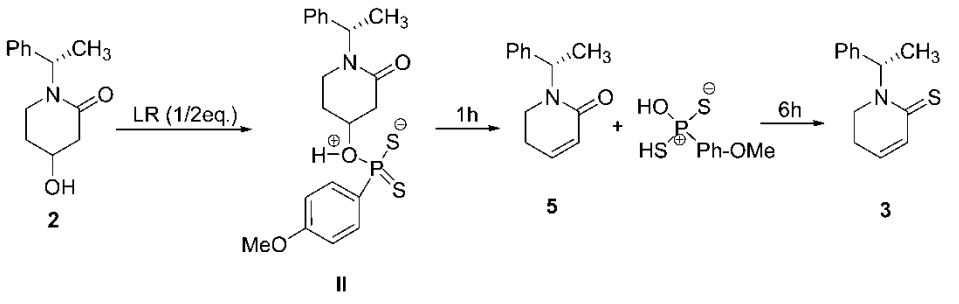
In the second procedure, a suspension of LR (1 eq.) in toluene was refluxed until its total dissolution occurred and the solution was cooled to 40 °C. To this solution was slowly added a solution of **2** (1 eq.) in toluene and the mixture reaction was refluxed during 1 h to give **3** in 90% yield. However, when this reaction was carried out in benzene, **3** was afforded in 25% and the diastereomeric mixture (1′*S*)-4-mercapto-1-(1′-phenylethyl)-piperidine-2-thione **4** was obtained as a 1:1 ratio and 75% yield. It is evident that when LR is refluxed in toluene or benzene, its dissociation into dithiophosphine yield (2 eq.) [6, 8] is favoured, which could explain the short time reactions and the high yields observed.

These results may be explained by assuming initial formation of the intermediate **I** [13], which in toluene (high-boiling point) generates **3** after the thionation of the amide function and the elimination of the 4-methoxyphenylphosphono dithioic acid [7, 8]. In contrast, intermediate **I** in benzene [12] (lower boiling point) favours the intramolecular reaction of the sulfur atom with C-4 and, by elimination of the 4-methoxyphenylphosphonothioic acid affords **4**. Scheme 1.



SCHEME 1

In order to examine if the formation of the products described above was dependent on the molar ratios of the reactants, this reaction was carried out using LR (0.5 eq.). To a solution of LR (0.5 eq.) in toluene was added compound **2** (1 eq.) and the mixture reaction was refluxed for 1 h to give the (1′*S*)-1-(1′-phenylethyl)-5,6-dihydropyridin-2(1*H*)-one **5** in 90% yield. However, when this reaction was refluxed for 6 h, compound **3** was generated in 90% yield. These results suggest that the dithiophosphine ylide first reacts with the hydroxyl group at C-4 to give **II** [13], and by elimination of the 4-methoxyphenylphosphono dithioic acid provides **5**. Finally, amide function of this compound reacts with the 4-methoxyphenylphosphono dithioic acid to afford **3**. Scheme 2.



SCHEME 2 Reagents and conditions: *i*, Lawesson's reagent (0.5 eq.) in toluene.

3. Conclusion

In conclusion, starting from diastereoisomeric mixture **2** have been prepared the compounds **3**, **4** and **5**. These compounds are interesting intermediates, which could be used as starting material in the enantioselective synthesis of alkaloids. In this sense, we are currently working on enantioselective synthesis of natural indolizidines and quinolizidines.

4. Experimental

^{1}H-NMR spectra were recorded with a Varian Unity instrument at 300 and 400 MHz, and ^{13}CNMR spectra at 75 and 100 MHz (tetramethylsilane as internal reference). IR spectra were obtained with a Nicolet FT-IR Magna 750 spectrometer. Chromatography was carried out using silica gel. Optical rotations were determined at room temperature with a Perkin-Elmer 341 polarimeter, using a 1 dm cell with a total volume of 1 mL and are referenced to the D-line of sodium. Mass spectra were recorded with a Jeol JEM-AX505HA instrument at a voltage of 70 eV.

4.1 *Reduction of the keto function of 2,4-diketopiperidone 1*

To a solution of compound **1** (0.2 g, 0.92 mmol) in MeOH (20 mL) at room temperature was added $NaBH_4$ (1.5 eq., 0.052 g, 1.38 mmol), then stirred during 8 h and concentrated *in vacuo*. The crude reactions was dissolved in dichloromethane, washed with brain solution, and the organic solution was dried with anhydrous Na_2SO_4, filtered, concentrated and purified by silica gel column chromatography (CH_2Cl_2:MeOH; 97:3) to yield the diasteroisomeric mixture **2** (198 mg, 95%).

4.2 *(1′S, 4R/4S)-4-Hydroxy-1-(1′-phenyl-ethyl)-piperidin-2-one 2*

υ_{max}/cm^{-1}: 3381 (w, OH), 1611 (s, CO); δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.52(3 H, d, 2′H), 1.78 (2H, m, 5H), 2.61 (2H, m, 6H), 3.0 (2H, m, 3H), 4.10 (1H, m, 4H), 6.03 (1H, q, 1′H), 7.19-7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$, Me_4Si): 16.07 (2′C), 31.27 (5C), 38.02 (6C), 41.68 (3C), 50.12 (1′C), 64.25 (4C), 126.6-139.3 (Ph-C), 167.71 (2C).

5. General procedure

5.1 *Thionation of 4-hydroxypiperidine-2-one 2*

A suspension of LR (0.275 g, 0.68 mmol, 1.0 eq) in dry toluene (40 mL) was refluxed until its total dissolution, then this solution was cooled at 40 °C and a solution of **2** (0.150 g, 0.68 mmol) in anhydrous toluene (20 mL) was added. The reaction was stirred during 1 h to give compound **3** in 90% yield, after purification by column chromatography (SiO_2, petroleum ether, petroleum ether:ethyl acetate). When this reaction was carried out in dry benzene and refluxed for 3 h, compound **3** was obtained in 25% yield, and the diastereoisomeric mixture **4** in 75% yield.

5.2 *(1′S)-(-)-1-(1′-Phenyl-ethyl)-5,6-dihydro-1H-pyridine-2-thione 3*

$[\alpha]_D^{22}$ -424.5 (*c* 1.0 in CH_2Cl_2); υ_{max}/cm^{-1}: 1619 (s, C=C), 1479 (s, C=S); δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.61(3 H, d, *J* 7.2, 2′H), 2.18 (2H, m, 5H), 3.15 (2 H, m, 6H), 6.2 (1 H, m, 4H), 6.62 (1H, dt, 3H), 7.1 (1H, q, *J* 7.2, 1′H), 7.19-7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$, Me_4Si): 14.56 (2′C), 24.03 (5C), 41.43 (6C), 56.89 (1′C), 127.16-139.53 (4C, 3C, Ph-C), 189.80 (2C). HRMS (FAB) calcd for $C_{13}H_{15}NS$: 217.3286: found: 217.3199.

5.3 *(1′S, 4R/4S)-(-)-4-mercapto-1-(1′-phenyl-ethyl)-piperidine-2-thione 4*

υ_{max}/cm^{-1}: 1496 (s, C=S); δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.60(3 H, m, 2′H), 1.79 (1 H, m, 5H), 2.12 (1H, m, 5H), 2.85 (1H, m, 6H), 3.08 (1H, m, 3H), 3.20 (1H, m, 4H), 3.38 (1H, m, 6H), 3.55 (1H, m, 3H), 7.23 (1H, m, 1′H), 7.28-7.36 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$, Me_4Si): 14.19 (2′C), 31.32 (4C), 32.67 (5C), 42.82 (6C), 51.64 (3C), 57.82 (1′C), 126.86-128.56 (Ph-C), 138.40 (*ipso*C), 196.78 (2C). HRMS (FAB) calcd for $C_{13}H_{17}NS_2$: 251.4099: found: 251.4053.

5.4 *Thionation of 4-hydroxypiperidine-2-one 2 with LR (0.5 eq.)*

A suspension of LR (0.137 g, 0.34 mmol, 0.5 eq.) in dry toluene (40 mL) was refluxed until its total dissolution, then this solution was cooled at 40 °C and a solution of **2** (0.150 g, 0.68 mmol) in anhydrous toluene (20 mL) was added. The reaction was stirred during 1 h to give compound **5** in 90% yield, after purification by column chromatography (SiO_2, petroleum ether, petroleum ether:ethyl acetate). When this reaction was refluxed for 6 h, afforded exclusively **3** in 90% yield.

5.5 *(1′S)-(-)-1-(1′-Phenyl-ethyl)-5,6-dihydro-1H-pyridin-2-one 5*

$[\alpha]_D^{22}$-67.6 (*c* 0.5 in CH_2Cl_2); υ_{max}/cm^{-1}: 1658 (s, NCO), 1604 (s, C=C); δ_H (400 MHz, $CDCl_3$, Me_4Si): 1.52(3 H, d, *J* 7.2, 2′H), 2.20 (2 H, m, 5H), 3.10 (2 H, m, 6H), 5.99 (1 H, m, 3H), 6.03 (1 H, q, *J* 7.2, 1′H), 6.50 (1H, m, 4H), 7.11-7.30 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$, Me_4Si): 15.70 (2′C), 24.40 (5C), 39.96 (6C), 49.45 (1′C), 125.56 (3C),127.11-140.50 (4C, Ph-C), 164.04 (2C). HRMS (FAB) calcd for $C_{13}H_{15}NO$: 201.2631: found: 211.2599.

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[12] Caution: benzene is a known carcinogen compound. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.
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